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(54) Title: SYNERGISTIC INSECTICIDAL COMPOSITIONS

(57) Abstract

The present invention provides a synergistic insecticidal composition comprising as essential active ingredients a neuronal sodium channel antagonist in combination with one or more compounds selected from the group consisting of pyrethroids, pyrethoid-type compounds, recombinant nucleopolyhedroviruses capable of expressing an insect toxin, organophosphates, carbamates, formamidines, macrocyclic lactones, amidinohydrazones, GABA antagonists and acetylcholine receptor ligands. Also provided are methods for synergistic insect control and crop protection.

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SYNERGISTIC INSECTICIDAL COMPOSITIONS

BACKGROUND OF THE INVENTION

Insecticidal agents and compositions have been developed to control insect pests such as agrohorticultural pests, hygienic pests, or wood-eating pests and in practice have been used as a single or a mixed agent. However, economically efficient and ecologically safe insect control compositions are still being sought. Insecticidal compositions which allow for reduced effective dosage rates, increased environmental safety and lower incidence of insect resistance are highly desirable. Although the rotational application of insect control agents having different modes of action may be adopted for good pest management practice, this approach does not necessarily give satisfactory insect control. Further, even though combinations of insect control agents have been studied, a high synergistic action has not always been found. Obtaining an insecticidal composition which demonstrates no cross-resistance to existing insecticidal agents, no toxicity problems and little negative impact on the environment is extremely difficult.

Therefore, it is an object of this invention to provide a synergistic insecticidal composition which demonstrates a high controlling effect with concomittant reduced crop production cost and reduced environmental load.

It is another object of this invention to provide methods for synergistic insect control and enhanced crop protection.

SUMMARY OF THE INVENTION

The present invention provides a synergistic insecticidal composition comprising as essential active ingredients a synergistically effective amount of a neuronal sodium channel antagonist in combination with one or more compounds selected from the group consisting of pyrethroids, pyrethroid-type compounds, recombinant nucleopolyhedroviruses capable of expressing an insect toxin, organophosphates, carbamates, formamidines, macrocyclic lactones, amidinohydrazones, GABA (gamma-aminobutyric acid) antagonists, and acetylcholine receptor ligands.

The present invention also provides a method for synergistic insect control which comprises contacting said insect with a synergistically effective amount of a neuronal sodium channel antagonist in combination with one or more compounds selected from the group consisting of pyrethroids, pyrethroid-type compounds, recombinant nucleopolyhedroviruses capable of expressing an insect toxin, organophosphates, carbamates, formamidines, macrocyclic lactones, amidinohydrazones, GABA antagonists and acetylcholine receptor ligands.

The present invention further provides a method for the enhanced protection of plants from infestation and attack by insects.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

" Acetylcholine receptor ligand compound " as used in this application means a compound which is capable of binding to the acetylcholine receptor site.

" Group A " as used in this application means insecticidal

1) pyrethroid compounds;
2) pyrethroid-type compounds;
3) recombinant nucleopolyhedroviruses capable of expressing an insect toxin;
4) organophosphate compounds;
5) carbamate compounds;
6) formamidine compounds;
7) macrocyclic lactone compounds;
8) amidinohydrazone compounds;
9) GABA antagonist compounds; and
10) acetylcholine receptor ligand compounds.

" Haloalkyl" as used in this application means an alkyl group C_xH_{2x+1} having 1 to 2x+1 halogen atoms which may be the same or different. Similarly, the terms " haloalkenyl" , " haloalkynyl" , " haloalkoxy " , " halophenyl" and the like mean mono- to perhalogen substitution wherein the halogens may be the same or different.

" Halogen " as used in this application means Cl, Br, I or F.

" Neuronal sodium channel antagonist" as used in this application means a compound which is capable of preventing the ability of a neuron cell to transfer sodium ions across the cell membrane.

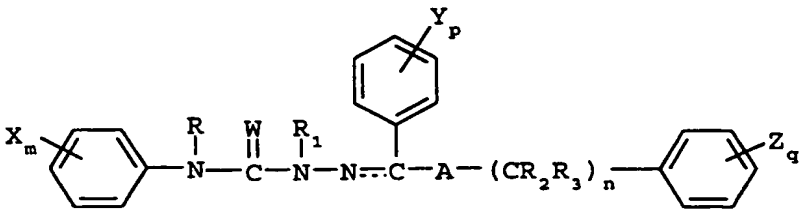
" Pyrethroid-type compounds " as used in this application means those compounds characterized by a non-ester linked aryl-phenoxybenzyl moiety.

" Synergism " as used in this application means a cooperative action encountered in a combination of two or more biologically active components in which the combined activity of the two or more components exceeds the sum of the activity of each component alone.

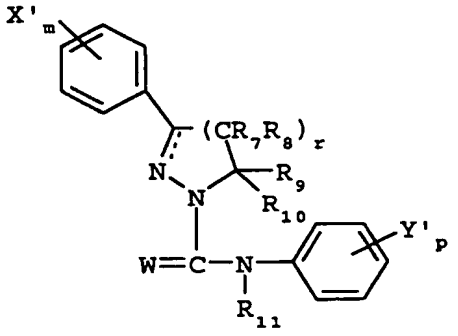
Surprisingly, it has now been found that a composition which comprises a combination of a neuronal sodium channel antagonist and a second insecticidal ingredient provides superior insect control at lower levels of the combined active agents than may be achieved when the neuronal sodium channel antagonist or the second insecticidal ingredient is applied alone.

As previously stated, the term neuronal sodium channel antagonist designates a compound which is capable of preventing the ability of a neuron cell to transfer sodium ions across the cell membrane. A neuron cell thus affected is unable to fire, resulting in paralysis, and ultimately mortality, in the target host. Descriptions of neuronal sodium channel antagonists and their mode of action may be found in Pesticide Biochemistry and Physiology, 60: 177-185 or Archives of Insect Biochemistry and Physiology, 37: 91-103.

Neuronal sodium channel antagonists include compounds such as those described in U.S. 5,543,573; U.S. 5,708,170; U.S. 5,324,837 and U.S. 5,462,938, among other publications. Exemplary of the neuronal sodium channel antagonist compounds useful in the composition of this invention are those compounds having the structural formula



(I)



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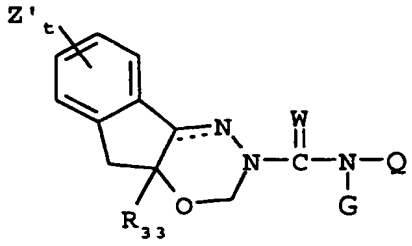


(III)

wherein A is CR_4R_5 or NR_6;

W is O or S;

X, Y, Z, X', Y' and Z' are each independently H; halogen; OH; CN; NO_2; C_1-C_6alkyl optionally substituted with one or more halogen, C_1-C_3alkoxy, C_1-C_3haloalkoxy, C_3-C_6cycloalkyl, C_2-C_6alkenyloxy or sulfonyloxy groups;

C_1-C_6alkoxy optionally substituted with one or more halogen, C_1-C_3alkoxy or C_3-C_6cycloalkyl groups;

C_1-C_6alkoxycarbonyl, C_3-C_6cycloalkylcarbonyloxy, phenyl optionally substituted with one or more halogen, C_1-C_4alkyl, or C_1-C_4alkoxy groups;

aminocarbonyloxy optionally substituted with one or more C_1-C_3alkyl groups; C_1-C_6alkoxycarbonyloxy; C_1-C_6alkylsulfonyloxy; C_2-C_6alkenyl; or $NR_{12}R_{13}$;

m, p and q are each independently an integer of 1, 2, 3, 4, or 5;

n is an integer of 0, 1 or 2;

r is an integer of 1 or 2;

t is an integer of 1, 2, 3 or 4;

R, R_1, R_2, R_3, R_4 and R_5 are each independently H or C_1-C_4alkyl;

R_6 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxyalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl, C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_1-C_6alkoxy-carbonyl, C_1-C_6alkylthio, or C_1-C_6haloalkylthio;

R_7 and R_8 are each independently H; halogen; C_1-C_6alkyl; C_1-C_6alkylcarbonyloxy; or phenyl optionally substituted with one or more halogen, CN, NO_2, C_1-C_6alkyl, C_2-C_6halo-alkyl, C_1-C_6alkoxy or C_1-C_6haloalkoxy groups;

R_9 and R_{10} are each independently H, or C_1-C_4alkyl;

R_{11} is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_4alkyl-carbonyl, C_1-C_6alkoxycarbonyl, or C_1-C_6halo-alkoxycarbonyl;

R_{12} and R_{13} are each independently H or C_1-C_6alkyl;

G is H; C_1-C_6alkyl optionally substituted with one or more halogen, C_1-C_4alkoxy, C_1-C_6haloalkoxy, CN, $NO_2S(O)_uR_{14}$, COR_{15}, CO_2R_{16}, phenyl or C_3-C_6cycloalkyl groups; C_1-C_6alkoxy; C_1-C_6haloalkoxy; CN; NO_2; $S(O)_uR_{17}$; COR_{18}; CO_2R_{19}; phenyl optionally substituted with one or more halogen, CN, C_1-C_3halo-

alkyl, or C_1-C_3haloalkoxy groups;
C_3-C_6cycloalkyl; or phenylthio;
Q is phenyl optionally substituted with one or more halogen, CN, SCN, NO_2, $S(O)_uR_{20}$, C1-C_4alkyl,
C_1-C_4haloalkyl, C_1-C_4alkoxyalkyl, C1-C_6alkoxy, C_1-C_6haloalkoxy, or $NR_{21}R_{22}$ groups;
u is an integer of 0, 1 or 2;
R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, R_{21} and R_{22} are each independently H or C_1-C_6alkyl;
R_{17} and R_{20} are each independently C_1-C_6alkyl or C_1-C_6haloalkyl;
R_{33} is CO_2R_{34};
R_{34} is H, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl or halophenyl; and the dotted line configuration C⋯N represents a double bond or a single bond (i.e. C-N or C=N); or

a stereoisomer thereof.

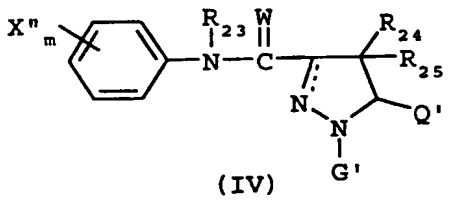
Preferred neuronal sodium channel antagonists suitable for use in the composition of the invention are those compounds of formula I, II or III wherein the dotted line configuration C⋯N represents a double bond.

More preferred neuronal sodium channel antagonists suitable for use in the inventive composition are those compounds of formula I or formula III wherein the dotted line configuration represents a double bond.

Particularly preferred neuronal sodium channel antagonists useful in the composition of the invention are those compounds of formula I or formula III wherein W is O; X is trifluoromethoxy and is in the 4-position; Y is trifluoromethyl and is in the 3-position; Z is CN and is in the 4-position; A is CH_2; n is 0; m, p and q are each 1; R and R_1 are each H; Z. is C_1; R_{33} and G are each CO_2CH_3; Q is p-(trifluoromethoxy)phenyl; and the

dotted line configuration C⋯N represents a double bond; or a stereoisomer thereof.

Further neuronal sodium channel antagonist compounds include those described in U.S. 5,116,850 and U.S. 5,304,573, among other publications. Exemplary of further neuronal sodium channel antagonist compounds suitable for use in the composition of the invention are those compounds having structural formula



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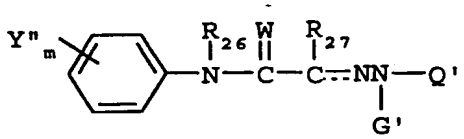


(V)

wherein W is O or S;

X' and Y' are each independently H; halogen; CN; SCN; C_1-C_6alkyl optionally substituted with one or more halogen, NO_2, CN, C_1-C_4alkoxy, C_1-C_4alkylthio, phenyl, halophenyl, C_1-C_4alkylsulfonyl, C_1-C_4haloalkylsulfonyl, or C_1-C_4alkoxycarbonyl groups; C_2-C_4alkenyl; C_2-C_4haloalkenyl; C_2-C_4alkynyl; C_2-C_4haloalkynyl; C_3-C_6cycloalkyl; C_3-C_6halocycloalkyl; phenyl optionally substituted with one or more halogen, CN, NO_2, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl or C_1-C_4haloalkylsulfonyl groups; C_1-C_4alkylcarbonyl; C_1-C_4haloalkylcarbonyl; or

$NR_{28}R_{29}$;

m is an integer of 1, 2, 3, 4 or 5;

G' is phenyl optionally substituted with one or more groups which may be the same or different selected from X';

a 5-membered heteroaromatic ring containing one or two heteroatoms selected from 0 or 1 oxygen, 0 or 1 sulfur and 0, 1 or 2 nitrogen atoms said 5-membered heteroaromatic ring being attached via carbon and being optionally substituted with one or more groups which may be the same or different selected from X'; or

a 6-membered heteroaromatic ring containing one or two heteroatoms selected from 0 or 1 oxygen, 0 or 1 sulfur and 0, 1 or 2 nitrogen atoms said 6-membered heteroaromatic ring being attached via carbon and being optionally substituted with one or more groups which may be the same or different selected from X';

Q' is H; C_1-C_6alkyl optionally substituted with one or more halogen, CN, C_1-C_3alkoxy, C_1-C_6alkoxycarbonyl, or phenyl optionally substituted with one or more halogen, CN, NO_2, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkylsulfonyl or C_1-C_4alkyl-sulfinyl groups;

C_2-C_6alkenyl; C_2-C_6alkynyl; or phenyl optionally substituted with one to three groups, which may be the same or different, selected from X';

R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and R_{29} are each independently H or C_1-C_4alkyl; and the dotted

line configuration C⁻⁻N represents a double bond or a single bond (i.e. C-N or C=N); or a stereoisomer thereof.

Further preferred neuronal sodium channel antagonist compounds of the invention are those compounds of formula IV or V wherein the dotted line configuration C⁻⁻N represents a double bond.

Other preferred neuronal sodium channel antagonist compounds suitable for use in the composition of the invention are those compounds of formula IV or V wherein W is O; X' and Y' are each independently H or C_1-C_6haloalkyl; m is 1; R_{23}, R_{24}, R_{25}, R_{26} and R_{27} are each H; G is phenyl optionally substituted with one or more halogen atoms; Q' is halophenyl or C_1-C_4alkyl optionally substituted with one phenyl or halophenyl group; and the dotted line configuration C⁻⁻N represents a double bond; or a stereoisomer thereof.

The second active ingredient of the insecticidal composition of the invention includes one or more compounds selected from Group A:

1) pyrethroid compounds which are known to be insecticidally active such as cypermethrin, cyhalothrin, cyfluthrin, permethrin or the like;

2) pyrethroid-type compounds which are known to be insecticidally active such as ethofenprox, silafluofen, or the like;

3) recombinant nucleopolyhedroviruses capable of expressing an insect toxin, preferably an insect neurotoxin such as Androctonus australis insect toxin (AaIT), for example HzNPV-AaIT;

4) organophosphate compounds which are known to be insecticidally active such as profenofos, acephate, sulprofos, malathion, diazinon, methyl parathion, terbufos, or the like;

5) carbamate compounds which are known to be insecticidally active such as methomyl, thiodicarb, fenothiocarb, or the like;

6) formamidine compounds which are known to be insecticidally active such as amitraz, chlordimeform, hydramethylnon, chlorfenamidine, or the like;

7) macrocyclic lactone compounds which are known to be insecticidally active such as spinosad, avermectin, emamectin, milbemectin, nemadectin, moxidectin or the like;

8) amidinohydrazone compounds which are known to be insecticidally active such as hydramethylnon;

9) GABA antagonist compounds which are known to be insecticidally effective such as fipronil, endosulfan, or the like;

10) acetylcholine receptor ligand compounds which are known to be insecticidally effective such as imidacloprid, acetamiprid, nitenpyram, thiamethoxam, or the like.

Descriptions of the above-listed commercially available compounds may be found in The Pesticide Manual, 11th Edition, British Crop Protection Council (1997) among other publications. Descriptions of recombinant nucleopolyhedroviruses capable of expressing an insect toxin include Treacy *et al*, Proceedings Beltwide Cotton Conference (1999), pp 1076-1083.

Preferred compositions of the invention are those compositions having a neuronal sodium channel antagonist compound of formula I or formula III in combination with one or more compounds selected from Group A.

More preferred compositions of the invention are those compositions having a formula I or formula III compound wherein W is O; X is trifluoromethoxy and is in

the 4-position; Y is trifluoromethyl and is in the 3-position; Z is CN and is in the 4-position; A is CH_3; n is 0; m, p and q are each independently 1; R and R_1 are each independently H; Z' is Cl; R_{33} and G are each independently CO_2CH_3; Q is p-(trifluoromethoxy)phenyl; and the dotted line configuration C--N represents a double bond in combination with one or more compounds selected from Group A.

Each of the compounds of formula I, II, III, IV and V embody assymetric centers which may be represented in the stereoisomeric R-form or S-form. The present invention also includes the R-form, the S-form or mixtures comprising the R-form and the S-form in an arbitrary ratio. For compounds of formula III, the S-form is preferred.

Advantageously, the neuronal sodium-channel antagonist compound of formula I, II, III, IV or V or a mixture thereof may be formulated with a second insecticidally effective ingredient and optionally other customary formulation adjuvants. Said formulation may be dispersed in a solid or liquid diluent for application to the insect, its food supply, breeding ground or habitat as a dilute spray or as a solid dust or dust concentrate.

The active ingredients of the inventive composition may also be formulated separately as a wettable powder, emulsifiable concentrate, aqueous or liquid flowable, suspension concentrate or any one of the conventional formulations used for insect control agents and tank-mixed in the field with water or other inexpensive liquid for application as a liquid spray mixture. The separately formulated compositions may also be applied sequentially.

Advantageously, the composition of the invention may be formulated as a bait composition comprising a

synergistically effective amount of a combination of a neuronal sodium channel antagonist plus one or more compounds selected from Group A and a solid or liquid edible nutritive substance. A preferred bait composition may contain by weight about 0.01% to 20% active ingredients, preferably a neuronal sodium channel antagonist in combination with hydramethylnon.

In actual practice, the composition of the invention may be applied to the plant foliage or plant stem or to the insect habitat or to the locus of a hygienic pest as a dilute spray prepared from any of the above-said formulations. The ratio of the essential active ingredients of the composition of the invention is about 1 weight part of a neuronal sodium channel antagonist to about 0.01-100 weight parts of one or more compounds selected from Group A.

The compositions of the invention are superior insecticidal compositions and are especially useful for the control of agrohorticultural pests, hygienic pests or wood-eating pests. Said compositions are highly effective for the protection of growing and harvested plants including: leguminous crops such as soybeans, snap beans, peas, wax beans and the like as well as cotton, forage crops, cole crops, leafy vegetables, tobacco, hops, tomatoes, potatoes, flowering ornamentals such as chrysanthemums, vine crops such as grapes, squash, pumpkin or melon and fruit trees such as cherry, peach, apple or citrus, from the ravages of insects.

The synergistic insecticidal composition of the invention is found to be highly active against a wide variety of lepidopteran and coleopteran insects such as *Helicoverpa zea* (cotton bollworm), *Heliothis virescens* (tobacco budworm), *Leptinotarsa decemlineata*(Colorado

potato beetle), *Diabrotica spp.* (corn rootworm) and the like.

Beneficially, the composition of the invention may be useful for the prevention and control of hygienic or public health pests such as: Diptera, e.g. houseflies, mosquitoes, or the like; Hymenoptera, e.g. ants, parasitic wasps, wasps or the like; Blattaria, e.g. cockroaches; or the like.

Further, the compositions of the invention may be particularly useful for the prevention and control of wood-eating insects such as termites (Isoptera), carpenter ants (Hymenoptera), wood-destroying beetles (Coleoptera) or the like.

These and other advantages of the invention may become more apparent from the examples set forth herein below. These examples are provided merely as illustrations of the invention and are not intended to be construed as a limitation thereof.

EXAMPLE 1

Evaluation of the Synergistic Insecticidal Effect of a Combination of a Neuronal Sodium Channel Antagonist Plus a Second Insecticide

In this evaluation, *Heliothis zea* (cotton bollworm), *Heliothis virescens* (tobacco budworm) and pyrethroid-resistant *Heliothis virescens* larvae used are obtained from laboratory colonies. Pyrethroid-resistant *H. virescens* are derived from the PEG-strain [Campannola & Plapp, Proceedings of Beltwide Cotton Conference (1988)].

Cotton leaves are immersed in 1:1 v/v, acetone/water solutions of test compound, or solutions of a combination of test compounds for a period of about 3 seconds. Following immersion, leaves are allowed to air-dry for 2-3 hours. Plastic bioassay trays containing multiple open-faced wells (4.0 x 4.0 x 2.5 cm) are used as the test arenas. Cut portions of a treated leaf, a moistened cotton dental wick and a single third-instar larva are placed into each well, covered with an adhesive vented clear plastic sheet and held under constant fluorescent light at about 27°C for a predetermined period of time. Larval mortality/morbidity is evaluated at 5 days after treatment. All treatments are replicated 4-5 fold in a randomized complete block design with 16-32 larvae per treatment. Using conventional log-probit analysis, the LC_{50} of each treatment is determined.

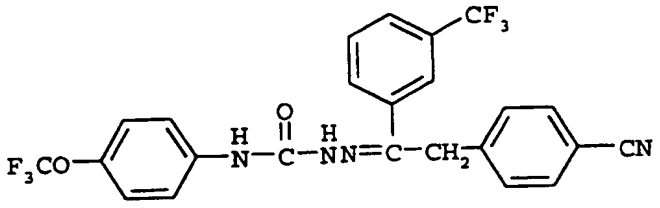
Using the above protocol, a neuronal sodium channel antagonist (Compound A) may be evaluated alone at dose rates of 0.1 ppm, 1.0 ppm and 10.0 ppm and in combination with 1.0 ppm of a second insecticidal

compound. Treatments which may be used are shown in Table I.

Table I

Second Active Compound	Dose Rate (ppm)	Compound A1 Dose Rate (ppm)	(ppm)	(ppm)	(ppm)
cypermethrin	0	0	0.1	1.0	10.0
	1.0	0	0.1	1.0	10.0
amitraz	0	0	0.1	1.0	10.0
	1.0	0	0.1	1.0	10.0
fipronil	0	0	0.1	1.0	10.0
	1.0	0	0.1	1.0	10.0
acetamiprid	0	0	0.1	1.0	10.0
	1.0	0	0.1	1.0	10.0
spinosad	0	0	0.1	1.0	10.0
	1.0	0	0.1	1.0	10.0
thiodicarb	0	0	0.1	1.0	10.0
	1.0	0	0.1	1.0	10.0

[1]Compound A = formula Ia neuronal sodium channel antagonist



(Ia)

EXAMPLE 2

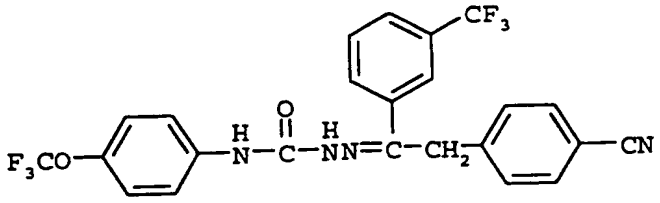
Evaluation of the Synergistic Insecticidal Effect Of a Combination Of A Neuronal Sodium Channel Antagonist Plus an Amidinohydrazone

In this evaluation, adult male German cockroaches (*Blattella germanica*) are used. For each test, a 4.0 g portion of ground Purina Dog Chow (Hi-Pro Glo®) is treated with an acetone solution of test compound alone or in combination with a second test compound. After treatment, the acetone is evaporated and the treated dog chow is placed in a 3/4 oz plastic cup which is placed in a harborage made of folded sheets of blotter paper placed in a plastic box (16" L x 11" W x 6" H). The plastic box (test arena) is also fitted with a 1 oz narrow mouth bottle with 2 dental wicks inserted at the mouth. A control box is prepared in the same manner using ground dog chow which has been treated with reagent grade acetone. Each treatment is replicated three times. Into each test arena are placed 20 healthy adult male cockroaches which have been reared in an insectary. The test arenas are then stored at 76°F and mortality is determined daily by visual examination. The data obtained are shown in Table II.

Table II

Test Compound	% Active Ingredien	% Mortality Days After Treatment 3	4	5	6	7	8
A[1]	0.05	0	0	0	0	0	0
A	0.10	1.7	11.7	11.7	11.7	18.3	18.3
A	0.50	5.0	5.0	5.0	5.0	5.0	5.0
B[2]	1.00	0	5.0	28.3	71.7	90.0	93.3
A+B	0.05+1.0	0	20.0	41.7	81.7	95.0	98.3
A+B	0.10+1.0	0	21.7	51.7	88.3	95.0	95.0
A+B	0.50+1.0	16.7	58.3	80.0	95.0	98.3	100.0
Control	0	0	1.7	3.3	3.3	3.3	5.0

[1]Compound A = formula Ia neuronal sodium channel antagonist
[2]Compound B = hydramethylnon



(Ia)

As can be seen from the data shown in Table II, combinations of a neuronal sodium channel antagonist plus an amidinohydrazone insecticide demonstrate synergistic insect control.

EXAMPLE 3

Evaluation of the Synergistic Insecticidal Effect Of a Combination Of A Neuronal Sodium Channel Antagonist Plus A Recombinant Nucleopolyhedrovirus Capable Of Expressing An Insect Toxin

In this evaluation, *Helicoverpa zea* (cotton bollworm) larvae are obtained from a laboratory colony. Test compounds are dissolved in 1:1 v/v acetone/water. Plastic bioassay trays (C-D International, Pitman, NJ) are used as test arenas. Each tray contains 32 open-faced wells, 4.0 x 4.0 x 2.5 cm. A portion (5 ml) of a wheat germ-soybean flour-based artificial diet (Southland Products, Lake Village, AR) is poured into each well. After the diet hardened, 0.4 ml of test solution is pipetted onto the diet surface in each well. Test solutions are evenly spread over surfaces of diet by picking up the tray and gently tilting it from side to side. Trays are then held in a vented area for about 2 h, until water is no longer pooled on diet surfaces. A single 4-day-old *H. zea larva* is then placed on the surface of diet in each well. After larval infestation, each well is covered with an adhesive, vented, clear plastic sheet.

All test arenas are held under constant fluorescent light and a temperature of about 27°C for duration of the assay. Larval mortality is determined at 2, 3, 4 and 7 days after treatment. A larva was considered to be dead if it exhibited little to no movement, even after being shaken in the diet tray. A total of 32 insects were tested for each treatment.

The data obtained are shown in Table III.

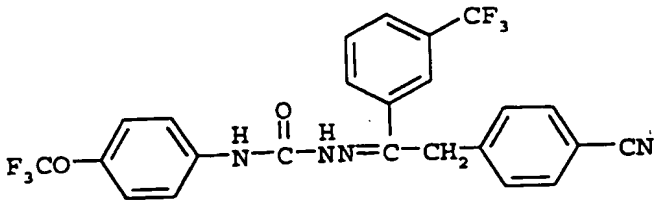
Table III

Test Compound	Conc. of Active Ingredient	% Mortality Days After Treatment 2	3	4	7
A[1]	0.1 ppm	43.8	46.9	53.1	53.1
B[2]	1000 OB[3]/ml	3.1	34.4	50.0	62.5
B	500 OB/ml	0.0	9.4	18.8	40.6
B	100 OB/ml	3.1	3.1	3.1	15.6
A+B	0.1+1000	87.5	90.6	93.8	96.9
A+B	0.1+500	75.0	78.1	84.4	87.5
A+B	0.1+100	62.5	75.0	75.0	78.1
Control	0	3.1	3.1	3.1	3.1

[1]Compound A = formula Ia neuronal sodium channel antagonist

[2]Compound B = HzNPV-AaIT, *Helicoverpa zea* Nucleopolyhedrovirus which expresses *Androctonus australis* insect toxin

[3]OB = viral occlusion bodies



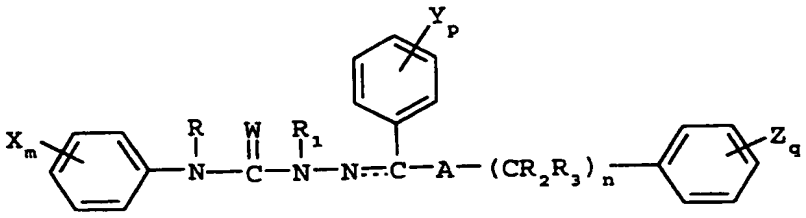
(Ia)

As can be seen from the data shown in Table III, combinations of a neuronal sodium channel antagonist plus a recombinant nucleopolyhedrovirus which is

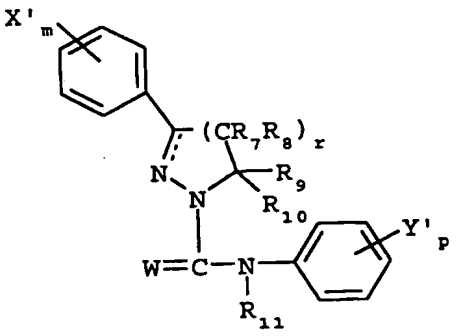
capable of expressing an insect toxin demonstrate synergistic insect control.

WHAT IS CLAIMED IS:

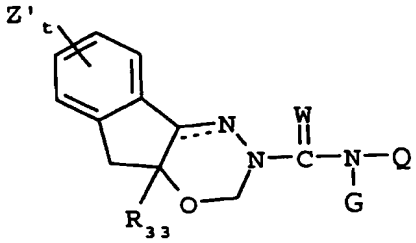
1. A synergistic insecticidal composition comprising a synergistically effective amount of a neuronal sodium channel antagonist in combination with one or more compounds selected from Group A wherein the neuronal sodium channel antagonist is a compound of formula



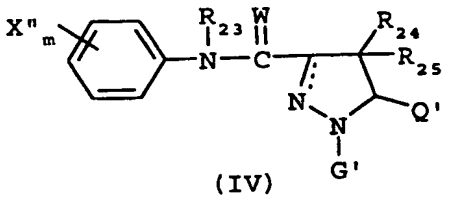
(I)



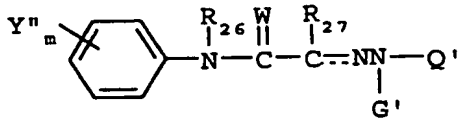
(II)



(III)



(IV)



(V)

wherein A is CR_4R_5 or NR_6;

W is O or S;

X, Y, Z, X', Y' and Z' are each independently H; halogen; OH; CN; NO_2; C_1-C_6alkyl optionally substituted with one or more halogen, C_1-C_3alkoxy, C_1-C_3haloalkoxy, C_3-C_6cycloalkyl, C_2-C_6alkenyloxy or sulfonyloxy groups;

C_1-C_6alkoxy optionally substituted with one or more halogen, C_1-C_3alkoxy or C_3-C_6cycloalkyl groups;

C_1-C_6alkoxycarbonyl, C_3-C_6cycloalkylcarbonyloxy, phenyl optionally substituted with one or more halogen, C_1-C_4alkyl, or C_1-C_4alkoxy groups;

aminocarbonyloxy optionally substituted with one or more C_1-C_3alkyl groups;

C_1-C_6alkoxycarbonyloxy; C_1-C_6alkylsulfonyloxy; C_2-C_6alkenyl; or $NR_{12}R_{13}$;

m, p and q are each independently an integer of 1, 2, 3, 4, or 5;

n is an integer of 0, 1 or 2;

r is an integer of 1 or 2;

t is an integer of 1, 2, 3 or 4;

R, R_1, R_2, R_3, R_4 and R_5 are each independently H or C_1-C_4alkyl;

R_6 is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkoxyalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, C_2-C_6alkenyl,

C_2-C_6alkynyl, C_1-C_6alkylcarbonyl, C_1-C_6alkoxy-carbonyl, C_1-C_6alkylthio, or C_1-C_6haloalkylthio;

R_7 and R_8 are each independently H; halogen; C_1-C_6alkyl; C_1-C_6alkylcarbonyloxy; or phenyl optionally substituted with one or more halogen, CN, NO_2, C_1-C_6alkyl, C_2-C_6haloalkyl, C_1-C_6alkoxy or C_1-C_6haloalkoxy groups;

R_9 and R_{10} are each independently H, or C_1-C_4alkyl;

R_{11} is H, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_4alkylcarbonyl, C_1-C_6alkoxycarbonyl, or C_1-C_6haloalkoxycarbonyl;

R_{12} and R_{13} are each independently H or C_1-C_6alkyl;

G is H; C_1-C_6alkyl optionally substituted with one or more halogen, C_1-C_4alkoxy, C_1-C_6haloalkoxy, CN, $NO_2S(O)_uR_{14}$, COR_{15}, CO_2R_{16}, phenyl or C_3-C_6cycloalkyl groups;

C_1-C_6alkoxy; C_1-C_6haloalkoxy; CN; NO_2; $S(O)_uR_{17}$; COR_{18}; CO_2R_{19}; phenyl optionally substituted with one or more halogen, CN, C_1-C_3haloalkyl, or C_1-C_3haloalkoxy groups;

C_3-C_6cycloalkyl; or phenylthio;

Q is phenyl optionally substituted with one or more halogen, CN, SCN, NO_2, $S(O)_uR_{20}$, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxyalkyl, C_1-C_6alkoxy, C_1-C_6haloalkoxy, or $NR_{21}R_{22}$ groups;

u is an integer of 0, 1 or 2;

R_{14}, R_{15}, R_{16}, R_{18}, R_{19}, R_{21} and R_{22} are each independently H or C_1-C_6alkyl;

R_{17} and R_{20} are each independently C_1-C_6alkyl or C_1-C_6haloalkyl;

R_{33} is CO_2R_{34};

R_{34} is H, C_1-C_6alkyl, C_1-C_6haloalkyl, phenyl or

halophenyl;

X' and Y' are each independently H; halogen; CN; SCN; C_1-C_6alkyl optionally substituted with one or more halogen, NO_2, CN, C_1-C_4alkoxy, C_1-C_4alkylthio, phenyl, halophenyl, C_1-C_4alkylsulfonyl, C_1-C_4haloalkylsulfonyl, or C_1-C_4alkoxycarbonyl groups; C_2-C_4alkenyl; C_2-C_4haloalkenyl; C_2-C_4alkynyl; C_2-C_4haloalkynyl; C_3-C_6cycloalkyl; C_3-C_6halocycloalkyl; phenyl optionally substituted with one or more halogen, CN, NO_2, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkoxy, C_1-C_4haloalkoxy, C_1-C_4alkylthio, C_1-C_4alkylsulfonyl or C_1-C_4haloalkylsulfonyl groups; C_1-C_4alkylcarbonyl; C_1-C_4haloalkylcarbonyl; or $NR_{28}R_{29}$;

G' is phenyl optionally substituted with one or more groups which may be the same or different selected from X' ;

a 5-membered heteroaromatic ring containing one or two heteroatoms selected from 0 or 1 oxygen, 0 or 1 sulfur and 0, 1 or 2 nitrogen atoms said 5-membered heteroaromatic ring being attached via carbon and being optionally substituted with one or more groups which may be the same or different selected from X' ; or

a 6-membered heteroaromatic ring containing one or two heteroatoms selected from 0 or 1 oxygen, 0 or 1 sulfur and 0, 1 or 2 nitrogen atoms said 6-membered heteroaromatic ring being attached via carbon and being optionally substituted

with one or more groups which may be the same or different selected from X' ;

Q' is H; C_1-C_6alkyl optionally substituted with one or more halogen, CN, C_1-C_3alkoxy, C_1-C_6alkoxycarbonyl, or phenyl optionally substituted with one or more halogen, CN, NO_2, C_1-C_4alkyl, C_1-C_4haloalkyl, C_1-C_4alkylsulfonyl or C_1-C_4alkyl-sulfinyl groups;

C_2-C_6alkenyl; C_2-C_6alkynyl; or phenyl optionally substituted with one to three groups, which may be the same or different, selected from X' ;

R_{23}, R_{24}, R_{25}, R_{26}, R_{27}, R_{28} and R_{29} are each independently H or C_1-C_4alkyl; and the dotted line configuration C---N represents a double bond or a single bond; or

a stereoisomer thereof.

2. The composition according to claim 1 wherein the neuronal sodium channel antagonist is a compound of formula I or III and the dotted line configuration C---N represents a double bond.

3. The composition according to claim 2 wherein W is O; X is trifluoromethoxy and is in the 4-position; Y is trifluoromethyl and is in the 3-position; Z is CN and is in the 4-position; A is CH_2; n is 0; m, p and q are each 1; R and R_1 are each H; Z' is Cl; R_{33} and G are each CO_2CH_3; and Q is p-(trifluoromethoxy)phenyl.

4. The composition according to claim 3 wherein the one or more compounds selected from Group A are

cypermethrin, cyhalomethrin, cyfluthrin, permethrin, ethofenprox, silafluofen, fipronil, endosulfon, imidacloprid, acetamiprid, nitenpyram, thiamethoxam, profenofos, acephate, sulprofos, malathion, diazinon, methyl parathion, terbufos, methonyl, thiodicarb, fenothiocarb, amitraz, chlordimeform, chlorfenamidine, avermectin, emamectin, milbemectin, nemadectin, or moxidectin.

5. The composition according to claim 3 wherein the one or more compounds selected from Group A is a recombinant nucleopolyhedrovirus capable of expressing insect toxin.

6. The composition according to claim 3 wherein the one or more compounds selected from Group A is hydramethylnon.

7. A method for synergistic insect control which comprises contacting said insect with a composition of any one of claims 1-6.

8. The method according to claim 7 wherein the insect is selected from the group consisting of Blattaria, Isoptera, Diptera, and Hymenoptera.

9. The method according to claim 8 wherein the insects are lepidoptera or coleoptera.

10. A method for protecting a plant from infestation and attack by insects which comprises applying to the foliage or stem of said plant a synergistically effective amount of a composition according to any one of claims 1-6.

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60/158,201	7 October 1999 (07.10.1999)	US

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Published:
— *With international search report.*
— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

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18 January 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 00/54591 A3

(54) Title: SYNERGISTIC INSECTICIDAL COMPOSITIONS

(57) Abstract: The present invention provides a synergistic insecticidal composition comprising as essential active ingredients a neuronal sodium channel antagonist in combination with one or more compounds selected from the group consisting of pyrethroids, pyrethoid-type compounds, recombinant nucleopolyhedroviruses capable of expressing an insect toxin, organophosphates, carbamates, formamidines, macrocyclic lactones, amidinohydrazones, GABA antagonists and acetylcholine receptor ligands. Also provided are methods for synergistic insect control and crop protection.

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 00/05879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A01N47/34 A01N47/38 A01N43/56 A01N37/50
//(A01N47/34,63:00,53:08,47:40,47:24,43:56,43:54,43:22,37:52)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, BIOSIS, CHEM ABS Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 33476 A (DU PONT ;MCAULIFFE DAVID (US); ANNAN ISAAC BILLY (US)) 18 September 1997 (1997-09-18) page 1 -page 2, line 20 page 4, line 19 - line 32 page 10, line 21 -page 11, line 22; claims ---	1-5,7-10
Y	HARDER, H. H. ET AL: "DPX-MP062: A novel broad-spectrum, environmentally soft, insect control compound" BRIGHTON CROP PROT. CONF.--PESTS DIS. (1996), (VOL. 2), 449-454, XP000925283 the whole document --- -/--	1-4,7-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 October 2000	09. 11. 2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	MÜLLNERS W.

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inten nal Application No
PCT/US 00/05879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 543 573 A (TAKAGI KAZUHIRO ET AL) 6 August 1996 (1996-08-06) cited in the application column 1, line 34 -column 2, line 5 table 3, compound A261 example 14 column 62, line 6 -column 63, line 2 column 64, line 56 - line 63	1-10
A	WO 97 40692 A (CIBA GEIGY AG ;SENN ROBERT (CH); MAIENFISCH PETER (CH); WYSS PETER) 6 November 1997 (1997-11-06) page 1 -page 4, line 2 page 9, compound CLXXXI claims 1,9	1-10
Y	B.F. MCCUTCHEN ET AL.: "Interactions of Recombinant and Wild-Type Baculovirus with Classical Insecticides and Pyrethroid-Resistant Tobacco Budworm (Lepidoptera: Noctuidae)" JOURNAL OF ECONOMIC ENTOMOLOGY, vol. 90, no. 5, October 1997 (1997-10), pages 1170-80, XP002142478 COLLEGE PARK, MD, US page 1170, the abstract page 1170, last paragraph -page 1171, paragraph 2; table 1 page 1177, paragraph 1 -page 1178, line 2 page 1179, last paragraph	1-5,7-10
P,A	WO 00 02453 A (NOVARTIS ERFINDUNGEN VERWALTUN ;NOVARTIS AG (CH); ARSLAN BIR MARTI) 20 January 2000 (2000-01-20) page 1 -page 4, paragraph 2 page 9, Nr.179 claim 1	1-10
X	"MIXTURES OF ARTHROPODICIDES AND FUNGICIDES" RESEARCH DISCLOSURE,GB,INDUSTRIAL OPPORTUNITIES LTD. HAVANT, no. 397, 1 May 1997 (1997-05-01), pages 361-363, XP000726479 ISSN: 0374-4353 the whole document	1-10
A	WO 96 03048 A (AMERICAN CYANAMID CO) 8 February 1996 (1996-02-08) page 1 -page 6, line 34 page 13, line 22 -page 14, line 18; claims page 11, line 1 - line 11 page 13, line 5 - line 12; example 2	1-10

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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/US 00/05879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 01055 A (UNIV CALIFORNIA) 18 January 1996 (1996-01-18) page 1 -page 4, line 9 page 10, last paragraph; claims	1-10
A	WO 93 00009 A (SCHERING AG) 7 January 1993 (1993-01-07) claims	1-4,6-10
A	GB 2 178 318 A (CIBA GEIGY AG) 11 February 1987 (1987-02-11) page 1, line 1 - line 35	1-4,6-10
A	US 4 163 102 A (LOVELL JAMES B) 31 July 1979 (1979-07-31) claims; examples 1,3,7	1-4,6-10

3

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/05879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [X] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

1-10 (as far as they cover subject-matter relating to items 1, 2 or 5; i.e. claims 1-4, 7-10 partially, claims 5 and 6 completely)

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ıal Application No
PCT/US 00/05879

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9733476 A	18-09-1997	AU 2327497 A	01-10-1997
		BR 9708025 A	27-07-1999
		CN 1213273 A	07-04-1999
		DE 69700781 D	16-12-1999
		DE 69700781 T	08-06-2000
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